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Synthesis of N-Benzyl-N-Methyl-β-Chloro-β(p-Chlorophenyl)-Ethylamine-Hydrochloride

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SYNTHESIS OF
N-BENZYL-N-METHYL-β-CHLORO-β(p-CHLOROPHENYL)-ETHYLAMINE-HYDROCHLORIDE

by

Van Saxton Hubbard UC 1967

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is approved by

Howard E Huffer

ACKNOWLEDGEMENTS

I wish to express my gratitude to Dr. Howard E. Sheffer and Dr. William R. Stoll for their assistance and guidance.

TABLE OF CONTENTS

LIST OF TABLES AND ILLUSTRATIONS

INTRODUCTION

Classes of compounds often have similar characteristics and activities. However, it has been shown in pharmacological studies that a small change in a structure produced by a substitution of an atom or a group of atoms on the original compound may cause a marked change in biological activity. When a certain compound shows usefulness as a drug, many variations of this compound are studied to see if a more useful form can be made. Two characteristics looked for are (1) effectiveness, which includes the onset or how long before the drug takes effect, and the duration or how long the effect lasts, and (2) lack of toxicity.

HISTORICAL BACKGROUND

N-benzyl-N-methyl-β-chloro-β(p-chlorophenyl)ethyl-amine-hydrochloride is classified as a member of the group of beta-haloalkylamines. This type of compound is known to have the characteristics of adrenergic blocking drugs. The beta-haloalkylamine series of adrenergic blocking compounds were introduced by Nickerson and Associates in 1946 (1). The series has several distinct characteristics which distinguish it from other adrenergic blocking compounds. Some of these characteristics are (1)

(1) they possess a high degree of chemical reactivity by liberating their beta halogen and forming a highly reactive ethylenimmonium intermediate.

(2) the ethylenimmonium moiety is responsible for the production of the adrenergic blockade produced by beta-haloalkylamines.

(3) they are for the most part, non-competitive type blockers, in the fact that after an initial competitive period, they do not obey mass-action relationships.

(4) unlike members of other series of adrenergic blockers, the blockade produced is generally very long in duration, highly specific, and effective.

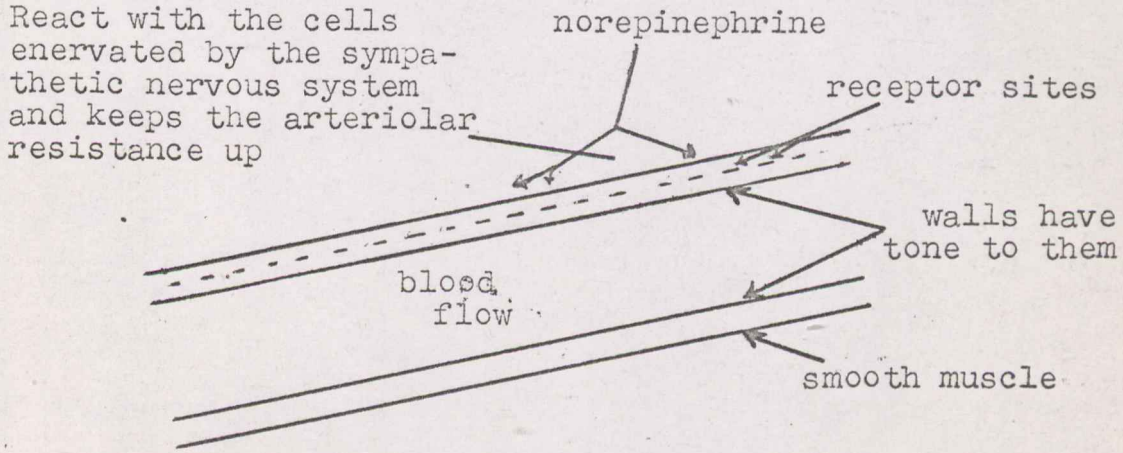
Nickerson has also established a list of structural requirements that a compound must meet in order to have blocking activity (2).

The compound:

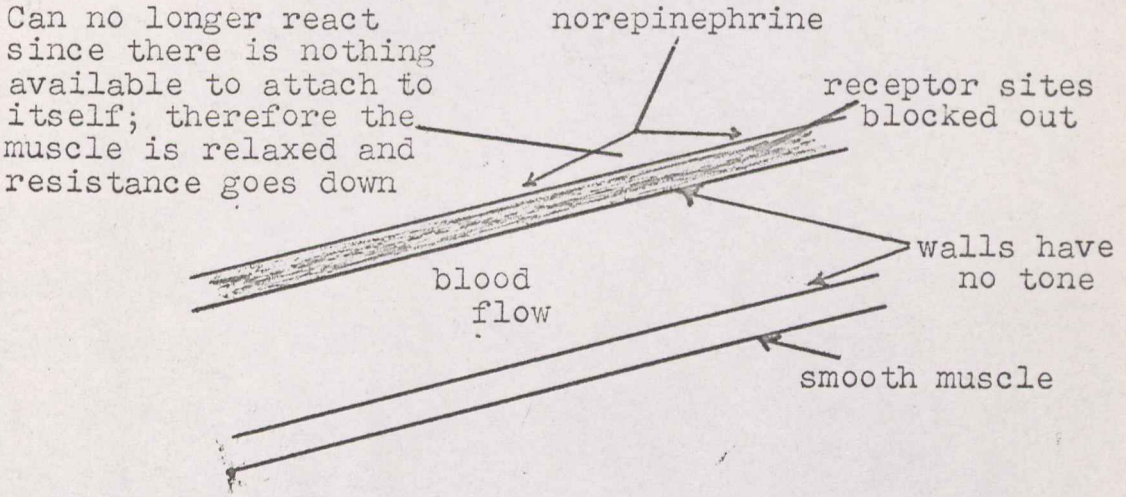
(1) "must be a tertiary amine or the quarternary derivative of an active amine."
(2) "must include at least one β-haloalkyl group capable of forming an intermediate ethylenimmonium (or vinyl) derivative with loss of the halogen."
(3) "must include an unsaturated ring structure attached to the nitrogen in such a way as to allow resonance stabilization of the active intermediate."
(4) "must not have any substitution on the aromatic ring of the benzyl group which tend to be out of the plane of the ring."

The compound is used to block the actions controlled by the sympathetic nervous system. An example of its function is shown in Figure 1. The drug in its intermediate form blocks the sympathetic nervous system and causes the smooth muscle to relax. One hoped for use of this type of compound is the relief of hypertension. At the present time, compounds which have desirable characteristics have had to be injected into the body near the location of the muscle to be affected due to the almost immediate formation of the active form. It is hoped that the compounds with similar properties can be formed which will enable them to be given orally and still produce the desired effect. Further research in this area should bring more knowledge of the receptor sites and their function in the body.

Figure 1



Before Adrenergic Blockade



After Adrenergic Blockade

The proposed compound and some of the previously studied β-haloalkylamines are shown in Figure 2. Some characteristics of these compounds are shown in Table 1.

Table 1

Experimental Results of Some β-haloalkyamines as Adrenergic Blocking Drugs(3)

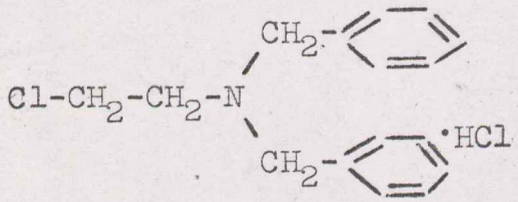
Compound	Onset	Duration
Dibenamine	2 hours	48 hours
Phenoxybenzamine	3/4 hours	24 hours
DMEA	1-2 minutes	1-2 hours
BMEA	2-5 minutes	17 hours

The various stages these compounds pass through are shown in Figure 3. Further knowledge of the chemistry of the reaction can be found by the study of the rate of formation of the chloride ion and the rate of thiosulfate uptake. The thiosulfate reacts rapidly with the intermediate formed but not with the parent compound (4).

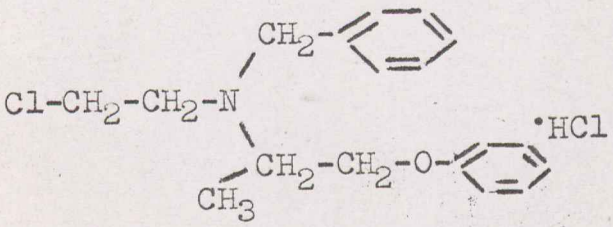
The scope of this thesis covers the attempted synthesis of N-benzyl-N-methyl-β-chloro-β(p-chlorophenyl)-ethylamine-hydrochloride.

Figure 2

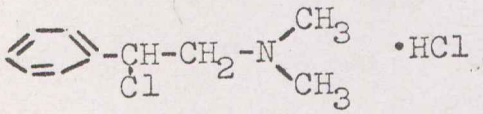
Structural Formulas of Some β-haloalkylamines Hydrochlorides



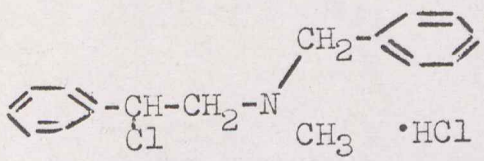
Dibenamine



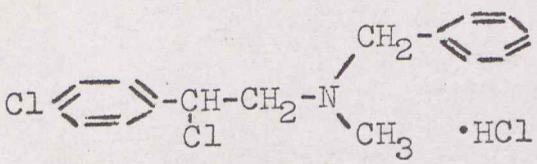
Phenoxybenzamine



N,N-dimethyl-β-chloro-β-phenylethylamine (DMEA)



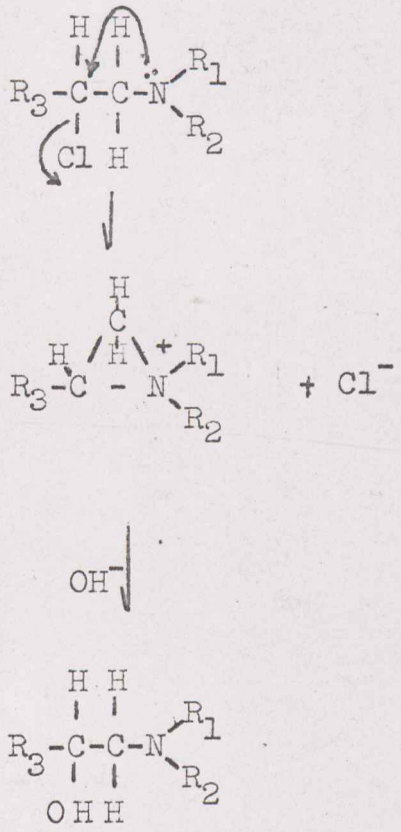
N-benzyl-N-methyl-β-chloro-β-phenylethylamine (BMEA)



N-benzyl-N-methyl-β-chloro-β(p-chlorophenyl)ethylamine

Figure 3

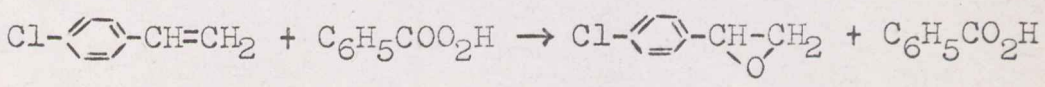
Reaction of β-haloalkylamines



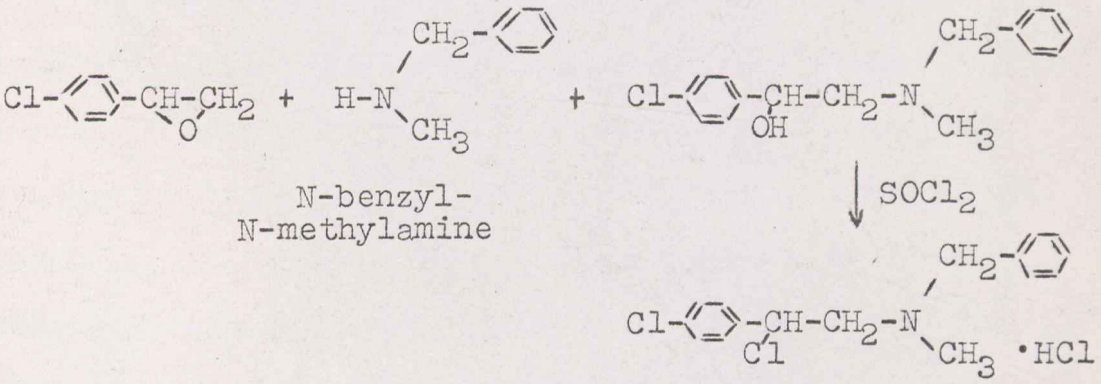
METHODS OF SYNTHESIS

Upon first viewing the problem of synthesizing N-benzyl-N-methyl-β-chloro-β(p-chlorophenyl)ethylamine-hydrochloride, two different methods of approach were considered. These approaches are

I.

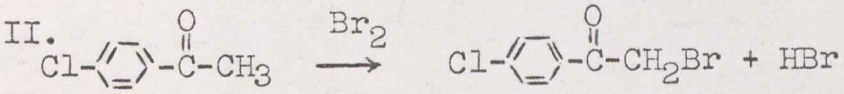


4-chlorostyrene perbenzoic acid 4-chlorostyrene oxide benzoic acid

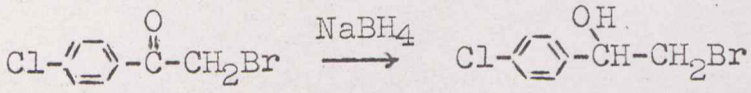


N-benzyl-N-methylamine

II.

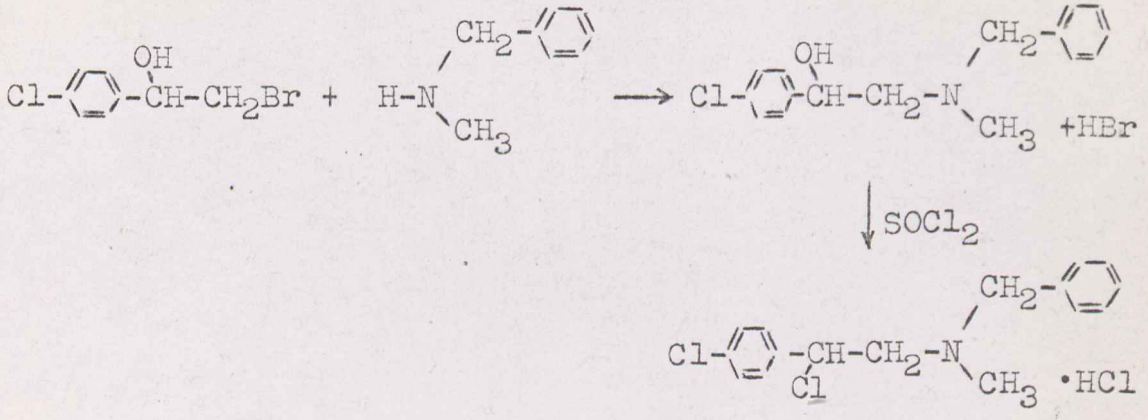


p-chloroacetophenone p-chlorophenacyl bromide



p-chlorostyrene bromohydrin

Method II (con't)



In the first method, it was not known whether the hydroxyl group would attach itself on the alpha or beta carbon in the reaction of 4-chlorostyrene oxide with N-benzyl-N-methylamine. Most likely the steric factor involving the bulky aromatic rings would prevent the undesired product from forming. Rather than try this method and take a chance on what would happen in the reaction, Method II was chosen.

EXPERIMENTAL RESULTS AND DISCUSSION

Preparation of p-chlorophenacyl bromide (sample 8-1) (5)

Bromine, 21.5 cc. (0.42 moles), was added at a rate of less than one cc. per minute to 65 grams (0.42 moles) of para-chloroacetophenone dissolved in fifty milliliters of pure anhydrous ether containing 0.5 grams of anhydrous aluminum chloride. The solvent and hydrobromic acid were removed by evaporation under reduced pressure and the crystalline product purified by washing with water and petroleum ether until only white crystals remained. Recrystallization from methanal gave 51.7 grams (52%) yield of p-chlorophenacyl bromide, melting point 87°C. (lit. 96.5°C.).

Preparation of para-chlorostyrene bromohydrin (6,7,8,9,10)

Sodium borohydride, 2.0 grams (0.055 moles), was added slowly to a mixture of 51.7 grams (0.22 moles) p-chlorophenacyl bromide and twenty-two milliliters methanol. The organic product was isolated by diluting with water, making acidic, and separating in a funnel. The product was diluted with anhydrous ether and dried over anhydrous sodium sulfate. The ether was removed by evaporation.

The addition of sodium borohydride to methanol

liberated hydrogen gas. The reaction was stopped and a NMR spectrum (sample 11-1, Figure 4) was made of the extracted product showing only fifty per cent reduction. Additional sodium borohydride was added and a second NMR spectrum (sample 11-2, Figure 5) was made of this product showing about ninety per cent reduction. The residue was an oily liquid, not completely free of solvents.

Preparation of N-benzyl-N-methyl-β-hydroxy-β(p-chlorophenyl) ethylamine (sample 13-1) (11)

The crude bromohydrin, 45 grams (0.192 moles), was reacted with 20 grams (0.17 moles) N-benzyl-N-methylamine for nineteen hours at about 100° C. After cooling, ten grams of sodium hydroxide in thirty milliliters of water were added followed by one hundred milliliters each of water and benzene and the mixture stirred mechanically for five minutes. A total of four benzene extractions was performed and the benzene layer dried with potassium carbonate. A vaccum distillation of the resulting mixture gave complete decomposition of the product.

At this point a revision of the initial procedure was undertaken. Since the trouble may have involved the reaction of the amine with the bromohydrin, an alternate path to the final product was devised. Instead


8.0
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6.0
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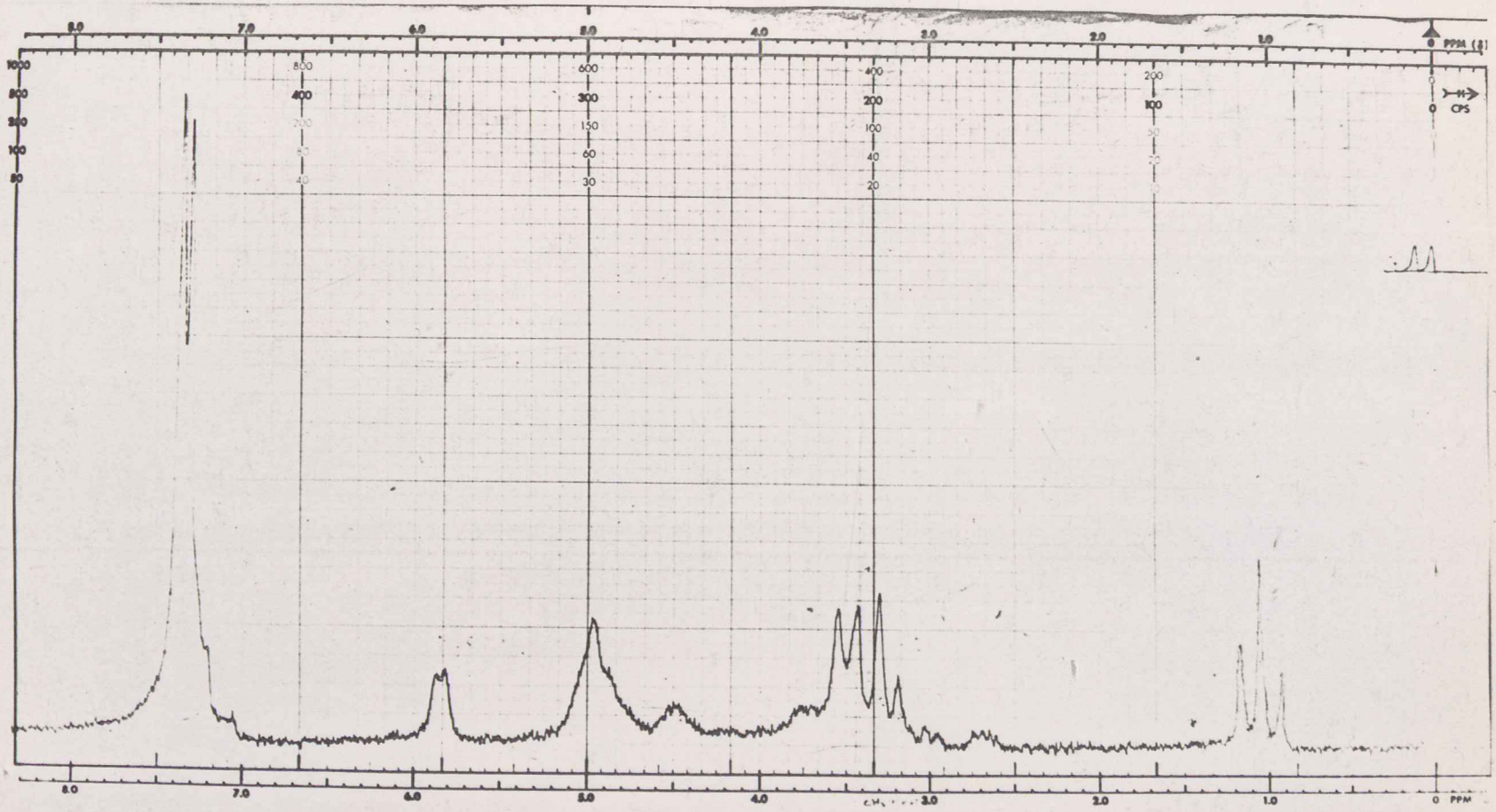
Figure 4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2.0
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CPS
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800
600
400
300
200
150
100
80
60
40
30
20
0 PPM

Figure 5

of reacting the amine with the bromohydrin, reaction with the p-chlorophenacyl bromide was tried. It was thought that since the substitution reaction probably proceeded by a SN_2 mechanism, the ω-bromine on the ketone would be more reactive than the bromine of the bromohydrin.

Second preparation of para-chlorophenacyl bromide (5)

The same procedure as before was used with the quantities of the reactants being doubled. Recrystallization from methanol gave 133.0 grams (67.8%) yield of para-chloro-phenacyl bromide, melting point 94° C. (lit. 96.5°).

A NMR of this product (sample 16-1) is shown in Figure 6.

A NMR of N-benzyl-N-methylamine was also made to aid in identification of later products (Figure 7).

Reaction of para-chlorophenacyl bromide and N-benzyl-N-methylamine (12)

N-benzyl-N-methylamine, 6.05 grams (0.05 moles), in twenty milliliters of ethanol was added dropwise to a solution of 11.7 grams (0.05 moles) para-chlorophenacyl bromide and 5.3 grams (0.05 moles) sodium carbonate in thirty milliliters of ethanol. The reaction was run for

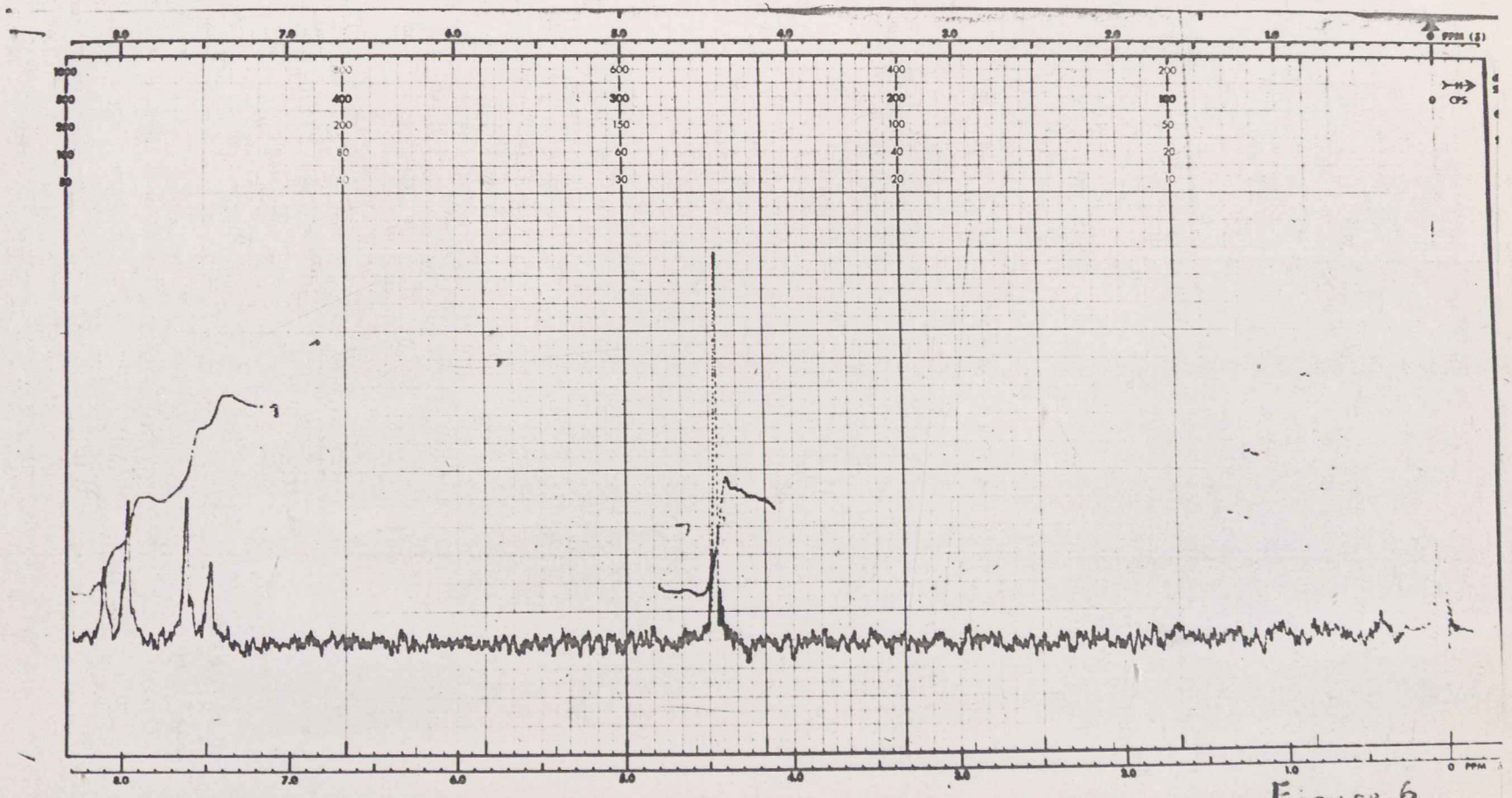


Figure 6

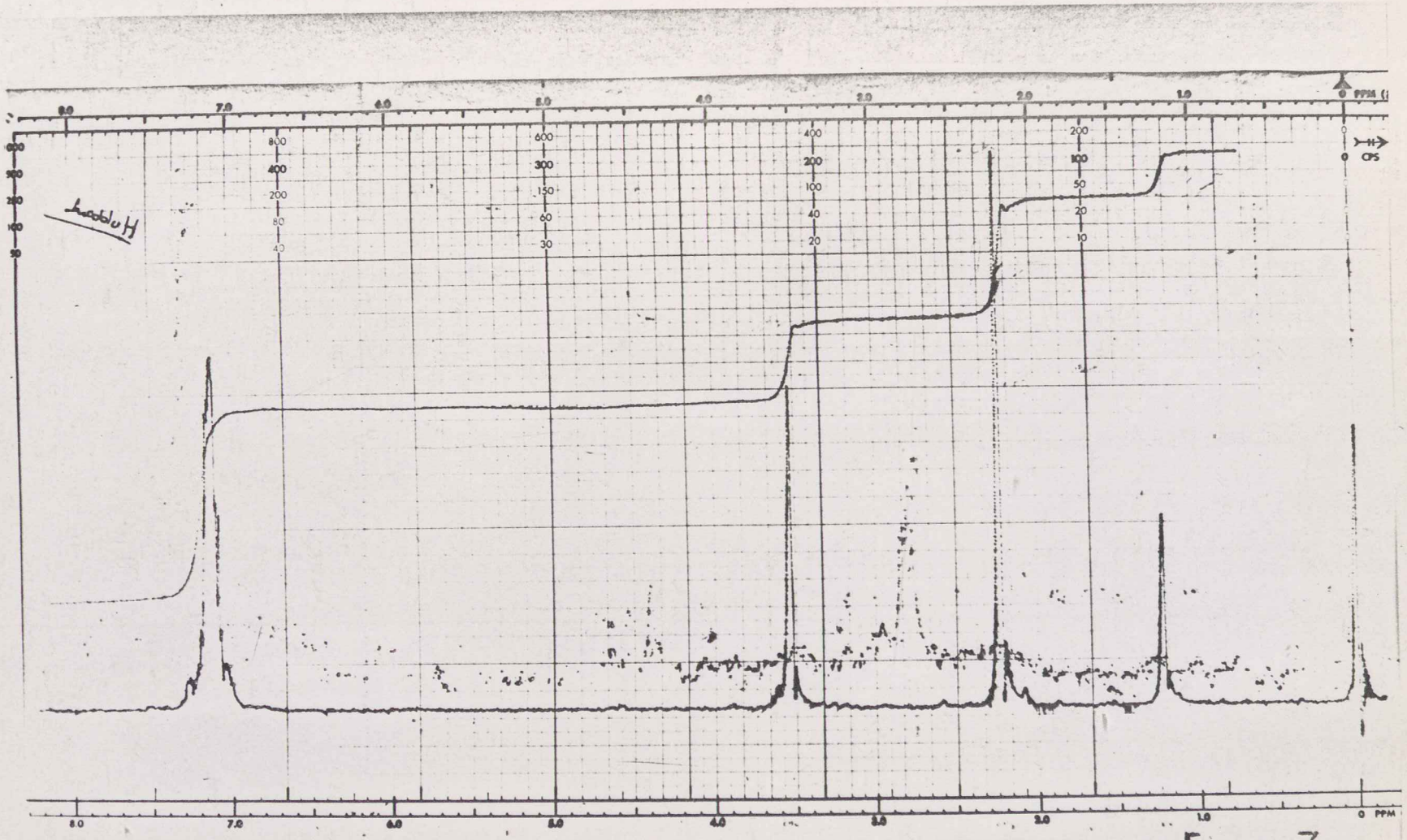


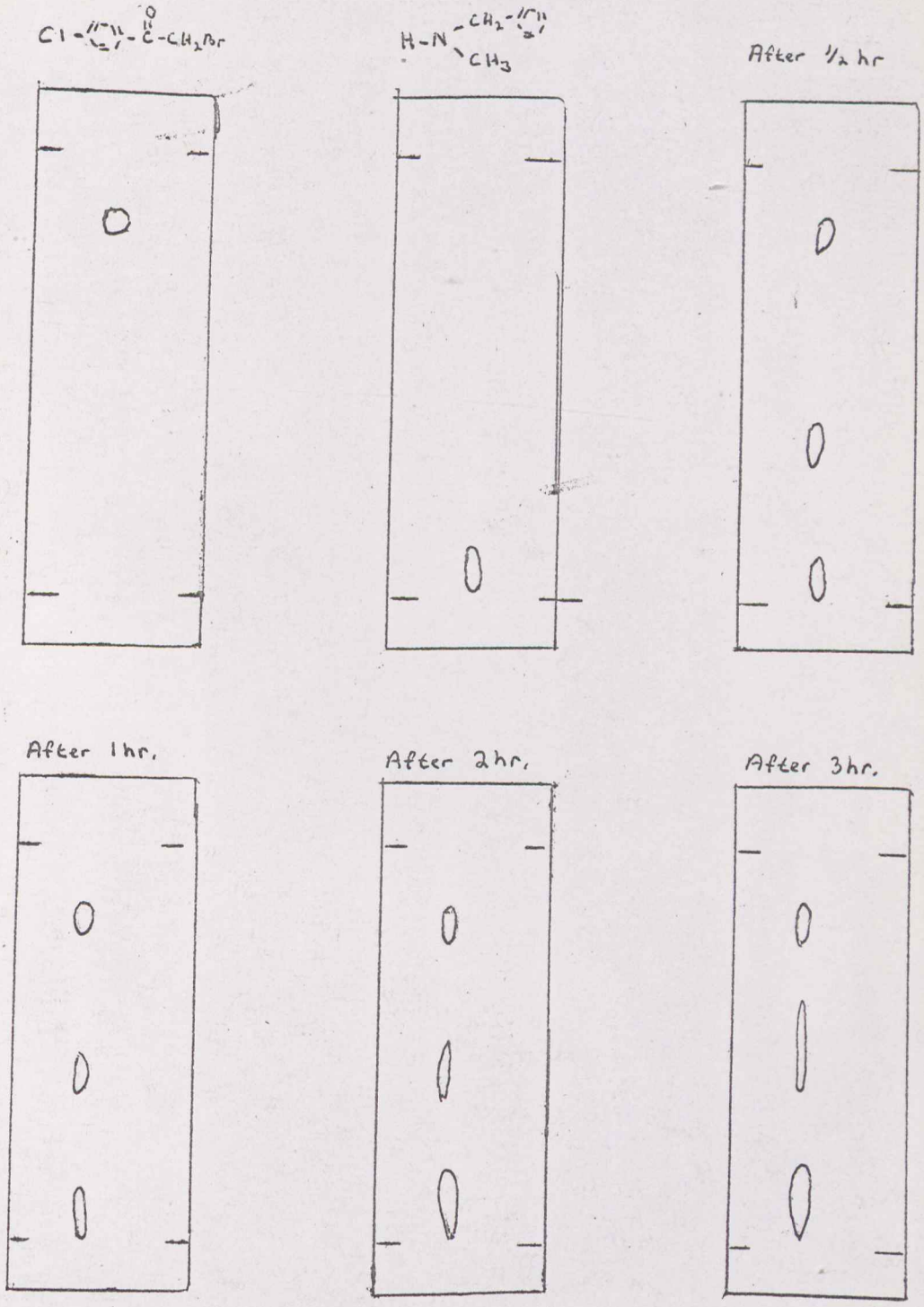
Figure 7

three hours at 60-70°C. The product was extracted with benzene and the benzene evaporated.

The reaction was followed by thin layer chromatography (Figure 8) which showed the presence of a third compound in the reaction mixture. However, the relative proportions of the three spots did not change with time indicating that the reaction did not go to completion. On cooling of the reaction mixture, a very viscous substance formed and a NMR spectrum (sample 18-2) (Figure 9) was made of the residue from the benzene extract. The NMR spectrum of sample 18-2 shows very little unreacted N-benzyl-N-methylamine. The two peaks at 4.4 and 4.6 ppm. are probably due to methylene between the carbonyl and the bromine of para-chlorophenacyl bromide on the one hand and the carbonyl and the nitrogen of N-benzyl-N-methyl-N-p-chlorophenacylamine on the other hand.

Since the substance remaining after evaporation of the benzene was a hard oily substance a problem of separation was confronted again. Recrystallization from ethyl acetate was tried but was unsuccessful. Therefore, the formation of the tertiary amine remained the troublesome step and a decision was made to return to the original procedure.

Figure 8


Cl-C6H4-C(=O)-CH2Br
H-N(CH3)-CH2-C6H5
After ½ hr
After 1hr.
After 2hr.
After 3hr.

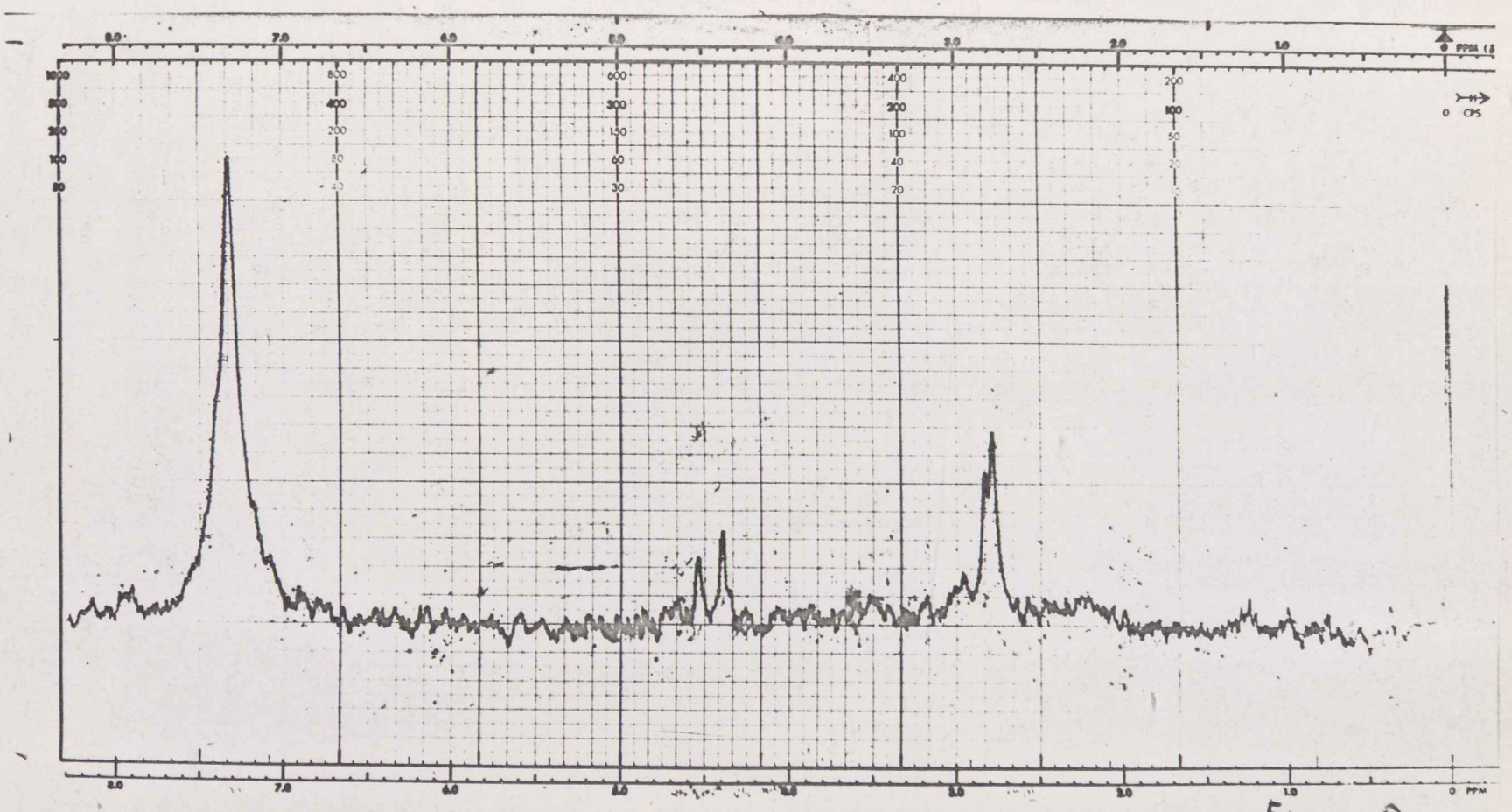


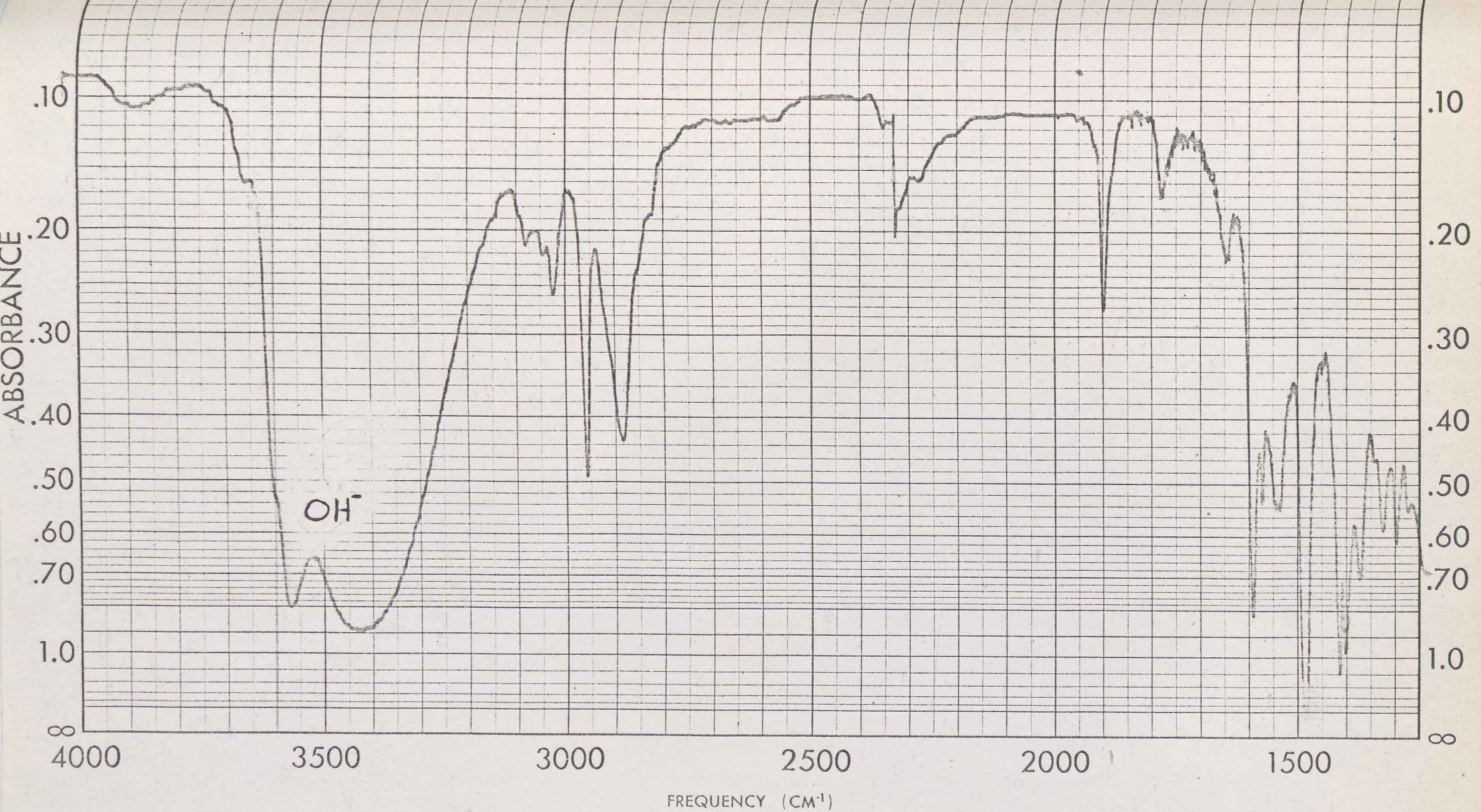
Figure 9

Second preparation of para-chlorostyrene bromohydrin

This time an excess of sodium borohydride, 3.03 grams (0.080 moles), was reacted with 45 grams (0.192 moles) para-chlorophenacyl bromide in thirty-three milliliters of methanol. White crystals of para-chlorostyrene bromohydrin, 42 grams (93%) melting point 54°C., was formed on acidification. The structure was verified by IR (Figures 10-13) and NMR (Figure 14) spectrums (sample 20-1).

Second preparation of N-benzyl-N-methyl-β-hydroxy-β (para-chlorophenyl) ethylamine

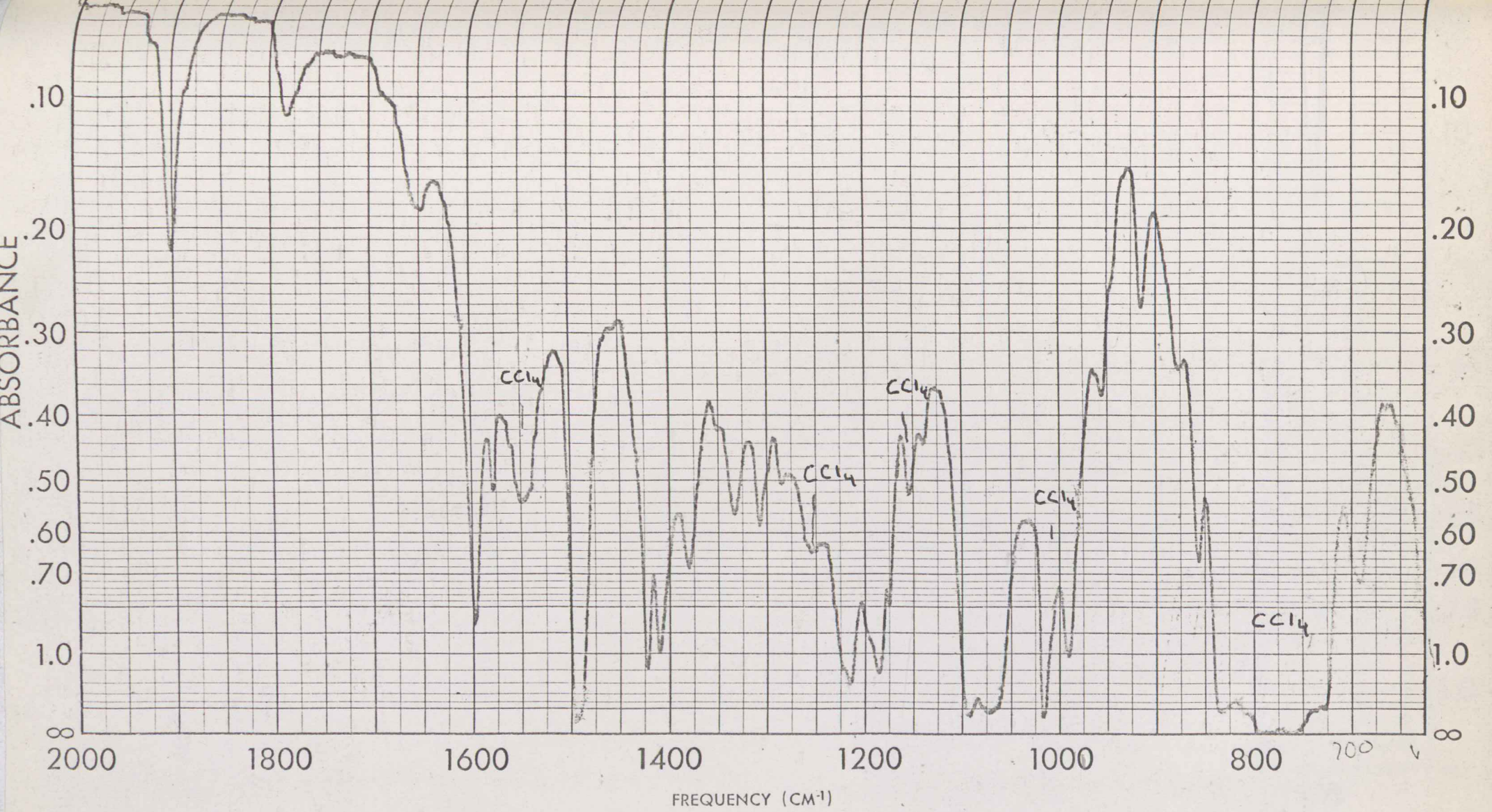
This time the reaction was run under an atmosphere of nitrogen for eight hours at 90-100° C., reacting 30 grams (0.128 moles) of bromohydrin with 15.6 grams (0.128 moles) of N-benzyl-N-methylamine. A hard oily substance was present after cooling. Sodium hydroxide, five grams, in thirteen milliliters of water was added followed by eighteen milliliters of water and twenty milliliters of benzene and the mixture stirred mechanically. Four benzene extractions were performed and the benzene layer dried using potassium carbonate, keeping the extracts under an atmosphere of nitrogen. The benzene was evaporated in a steam bath under reduced pressure.



SAMPLE Cl-C6H4-CH(OH)-CH2Br	CURVE NO.	SCAN SPEED Fast	OPERATOR V. H.
	CONC.	SLIT	DATE 2/29/67
ORIGIN Reaction Product 20-1	CELL PATH	REMARKS Figure 10	
SOLVENT CCl4	REFERENCE		

PART NO. 237-1032 ®

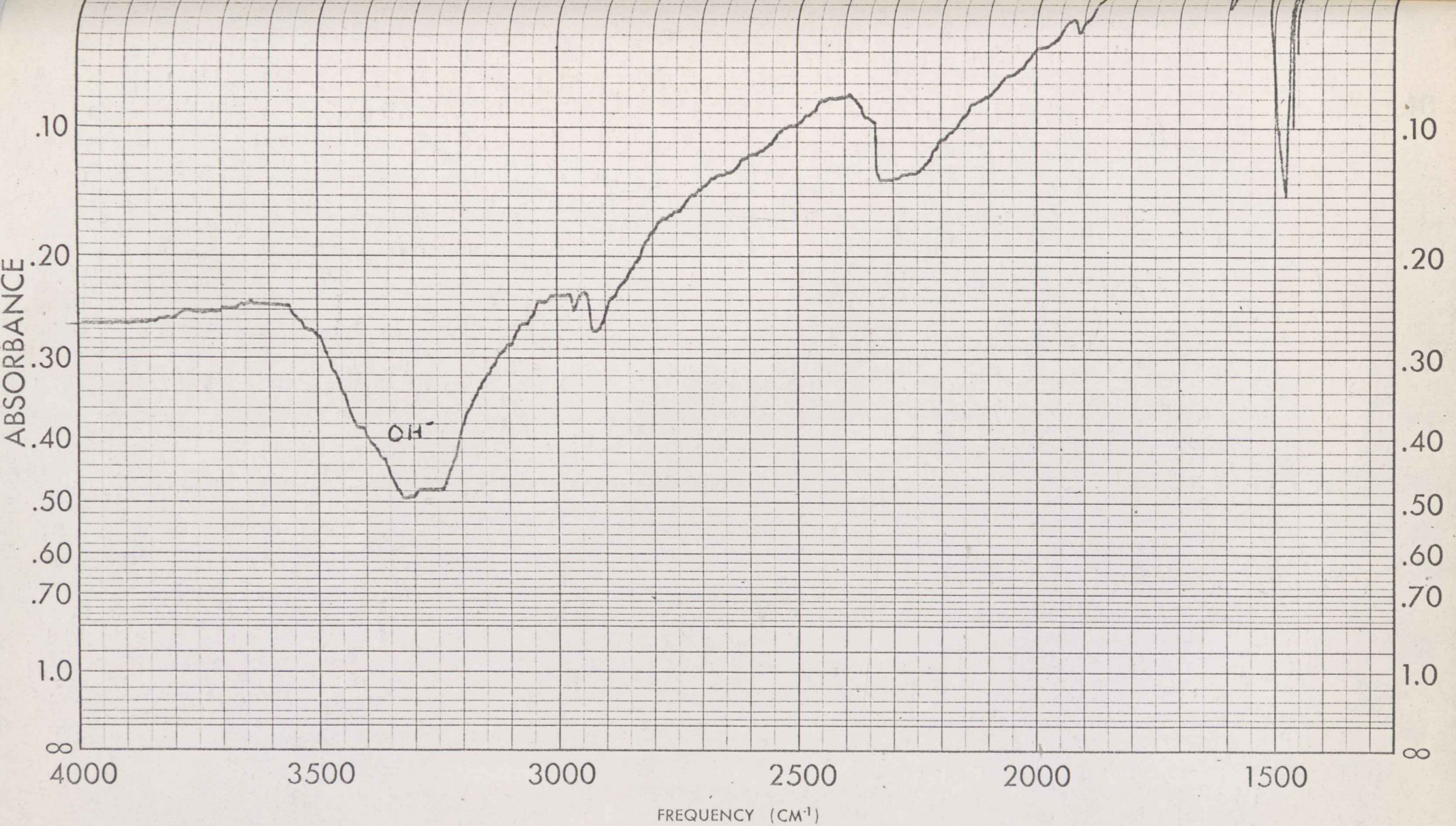
PERKIN-ELMER



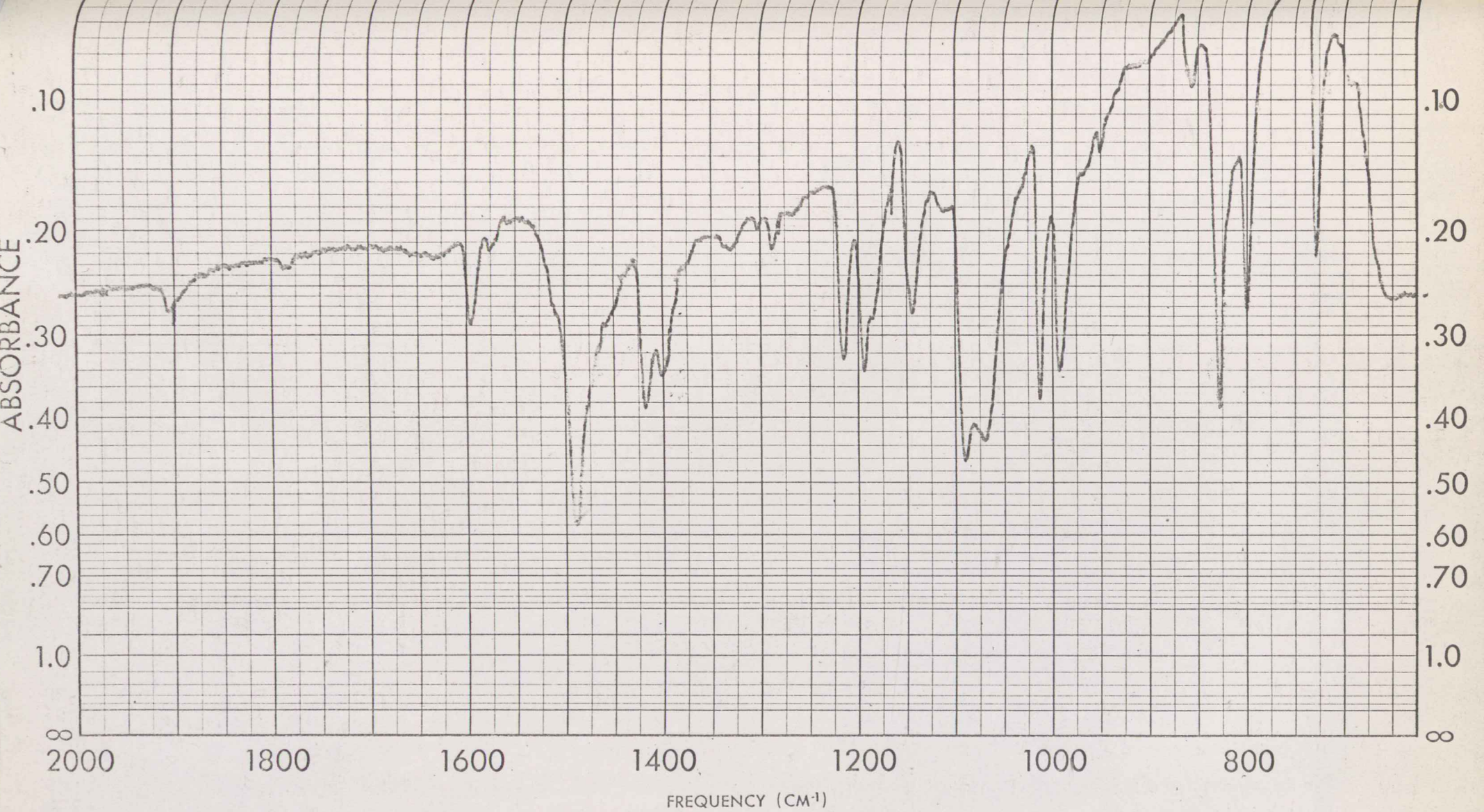
SAMPLE Cl-⟨=⟩-OH CH-CH2Br	CURVE NO.	SCAN SPEED	OPERATOR V. H.
	CONC.	SLIT	DATE 2/29/67
ORIGIN Reaction Product 20-1	CELL PATH	REMARKS Figure 11	
SOLVENT CCl4	REFERENCE		

PART NO. 237-1033 ®

PERKIN-ELMER



SAMPLE KBr Pellet of Cl-⟨=⟩-C(=O)CH₂Br	CURVE NO.	SCAN SPEED Fast	OPERATOR V.H
ORIGIN Reaction Product 20-1	CONC.	SLIT	DATE 2/10/67
SOLVENT	CELL PATH	REMARKS Figure 12	
	REFERENCE		



SAMPLE KBr Pellet of Cl-(C6H4)-CH(OH)-CH2Br	CURVE NO.	SCAN SPEED Fast	OPERATOR V.H.
	CONC.	SLIT	DATE 2/10/67
ORIGIN Reaction Product 20-1	CELL PATH	REMARKS Figure 13	
SOLVENT	REFERENCE		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0 CPS
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Figure 14

A small sample from the reaction mixture was taken before any additions were made. An attempt to recrystallize from a mixture of methanol and water resulted in a white viscous substance which was oxidized immediately by air. Since the method did not result in purification of the product, the chlorination step of the synthesis was performed without the isolation of the intermediate in hopes of obtaining a crystalline product.

Preparation of N-benzyl-N-methyl-β-chloro-β(para-chlorophenyl) ethylamine hydrochloride (13)

Thionyl chloride, 7.7 ml. (0.10 moles), was added dropwise to the crude reaction mixture from the last reaction in fifty milliliters of chloroform. No crystals appeared at the end of the reaction nor after two hundred milliliters of ethyl acetate was added and refluxed for one half hour.

It was decided to repeat the reaction of the bromohydrin and the amine and find a method of purification at this step.

Third preparation of N-benzyl-N-methyl-β-hydroxy-β(para-chlorophenyl) ethylamine

The reaction was run under the same conditions for eight hours, reacting 7.84 grams (0.0335 moles) of

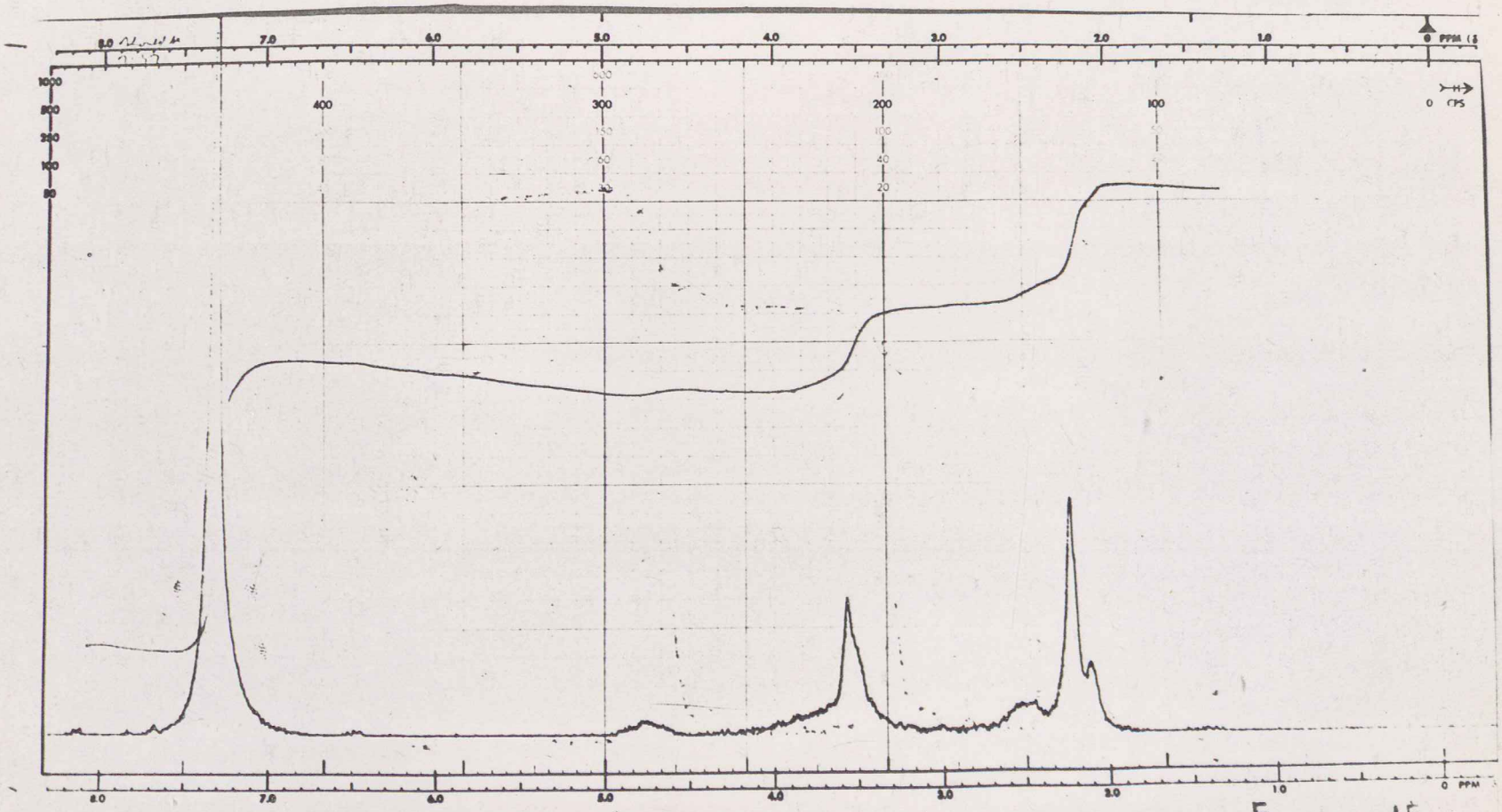
bromohydrin with 5.3 grams (0.0437 moles) of N-benzyl-N-methylamine. After cooling the solution, different methods of purification were attempted. A sample was dissolved in a small amount of benzene and a NMR spectrum (sample 30-1, Figure 15) was made. No conclusion could be drawn from this spectrum.

A sample (about 0.1 grams) was placed in ether and a white solid, melting point 164-166° C., formed. This solid was probably the hydrobromide of the desired product. Sodium hydroxide was added and the either and water layers separated, however, no product was recovered.

Twice, samples (about 2 grams each) were placed in ether, but each time a gummy substance was obtained, part of which was soluble in water. The water layer was decanted and the water evaporated, leaving white crystals, melting point 126-130° C., with much softening beforehand. Another method of recrystallization of the product was found and no more was done with these crystals.

A Hinsberg separation was applied to another two gram sample which showed the presence of a tertiary amine.

Another sample was washed in ether, dissolved in a minimum quantity of ethanol and recrystallized by the addition of ethyl acetate (14). White crystals formed having a sharp melting point of 166° C. The remainder of the reaction mixture (two grams) was washed with ether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0 PPM
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250
100
50
400
300
200
100
0 CPS
60
40
20
PPM

Figure 15

and recrystallized. A total of 0.749 grams from both samples was obtained.

The attainment of the hydrobromide has solved the major problem of this synthesis, namely the purification of a tertiary amine. This product can now be dissolved, taken up in ether and converted to the hydrochloride by gaseous HCl (15) and then treated with thionyl chloride (12) to obtain N-benzyl-N-methyl-β-chloro-β(para-chlorophenyl) ethylamine hydrochloride. To aid in future work on this problem a NMR spectrum (Figure 16) has been made for BMEA.

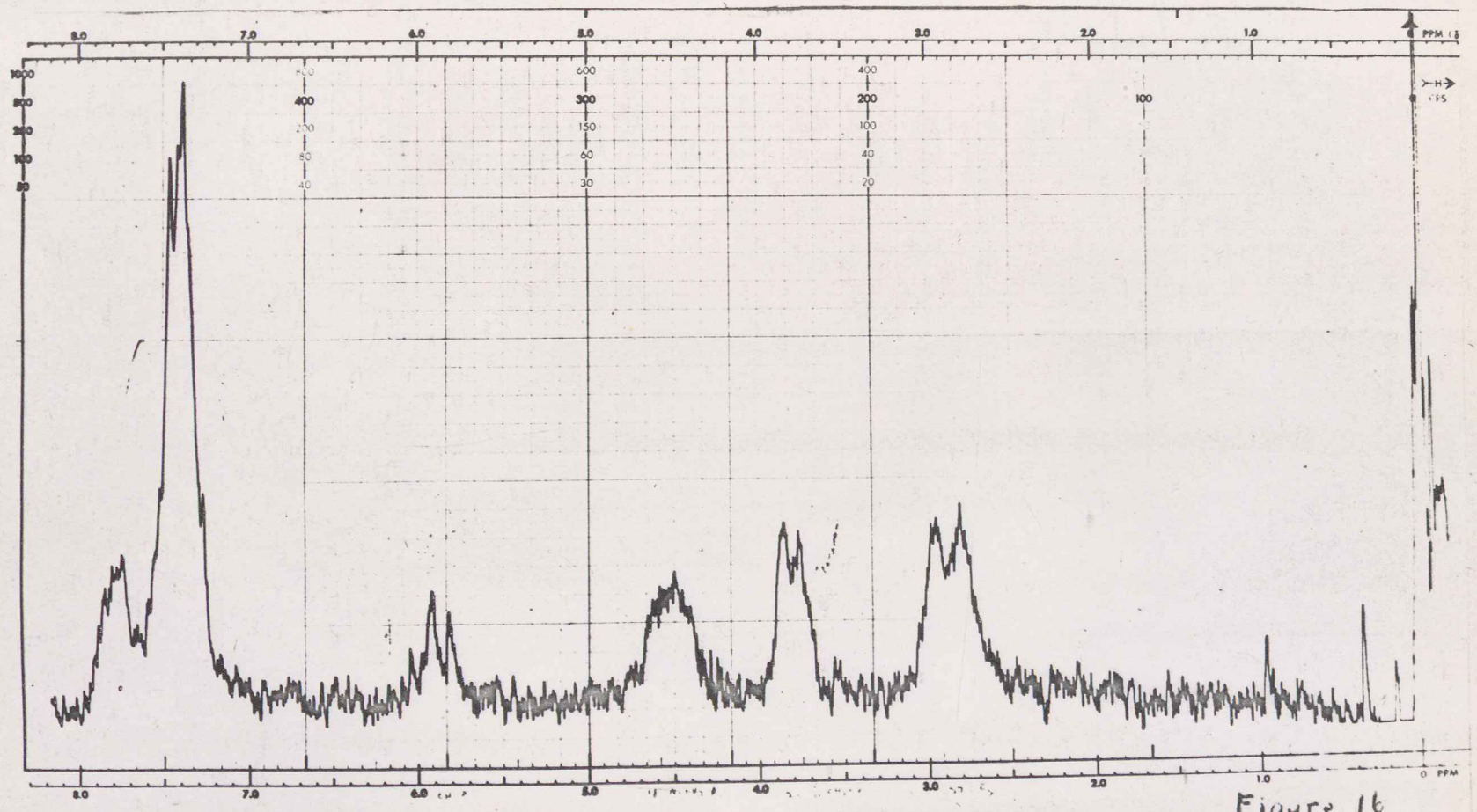

8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0 PPM
1000
800
600
400
300
200
150
100
60
40
30
20

Figure 16

SUMMARY

More difficulties than were originally expected occurred in the synthesis of N-benzyl-N-methyl-β-chloro-β(para-chlorophenyl) ethylamine hydrochloride. The major difficulty was the purification of the tertiary amine which was solved toward the end of the research period.

From correspondence with the Lilly Research Laboratories and the Bristol Laboratories (see appendix) our method of approach was the same as the commercial method. However, our conditions for the synthesis of tertiary amines were not as vigorous as theirs and in some cases we failed to use enough base to tie up the hydrobromic acid evolved.

Now that the method of synthesis has been solved, little trouble is expected in reaching the final product. It is hoped by this worker that the synthesis will be completed and the study of its physiological activity will be made.

APPENDIX A

Interpretation of NMR spectrums

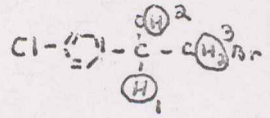
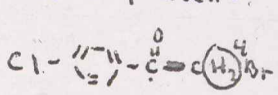
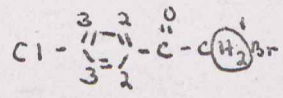
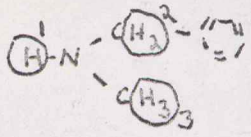
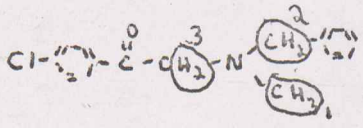
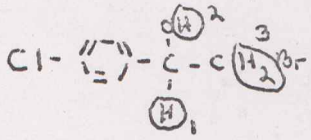
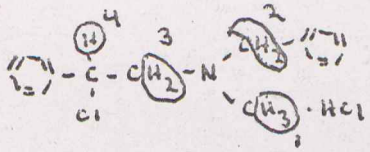
Figure #	Compound predicted	Peak(ppm)	Type of Hydrogen
4	sample 11-1	3.25	CH_3OH(solvent)
		3.5	3
		4.4	4
	also present	4.9	1
		5.8	2
		7.2	aromatic
5	sample 11-2	1.0	CH_3 group in ether
	Same as above	2.3	CH_2 group in ether
		3.5	3
		4.4	4
		4.9	1
		5.9	2
		7.3	aromatic
6	sample 16-1	4.45	1
		7.5, 8.0	2,3

Figure #	Compound predicted	Peak(ppm)	Type of Hydrogen
7		1.25	1
		2.2	3
		3.55	2
		7.15	aromatic
9	sample 18-2	2.8	1
		4.4	2
		4.55	3
		7.35	aromatic
14	sample 20-1	3.3	2
		3.5	3
		4.8	1
		7.3	aromatic
16		2.8	1
		3.8	3
		4.5	2
		5.9	4
		7.4	aromatic

Bristol LABORATORIES
Division of Bristol-Myers Company
SYRACUSE 1, NEW YORK

October 9, 1961

Frank C. Ferguson, Jr., M.D., Chairman
Department of Pharmacology
The Albany Medical College of Union University
Albany, New York

Dear Dr. Ferguson:

In response to your letter of September 26, we are happy to supply you with the attached method of perparation of N,N-dimethyl-p-chloro-phenethylamine hydrochloride.

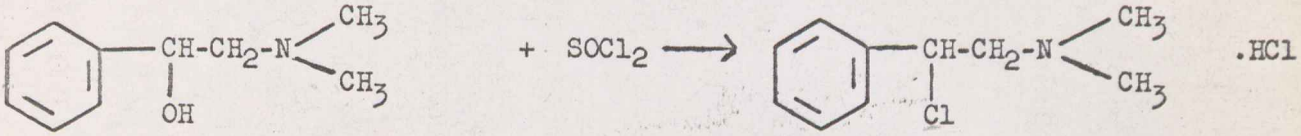
I believe the directions are fairly clear, however, if you have additional questions after going over it please do not hesitate to get in touch with us.

Sincerely yours,

H. Leo Dickison
Director of Laboratories

HLD/mal
Att.

Preparation of N,N-dimethyl-p-chloro-phenethylamine HCl



(165.23) (118.97) (220.14)

Materials:	N,N-dimethyl-β-hydroxy-phenethylamine	33 g. (0.2 mole)
	Thionyl chloride	18.8 ml. - 30.9 g. (0.26 mole)
	Chloroform	150 cc

Procedure: To a solution of the amino alcohol in 100 ml. of chloroform was added dropwise (with stirring) a solution of the thionyl chloride in 50 ml. of chloroform. At the end of the addition crystals appear and form a very thick mush. Then 250 ml. of ethyl acetate is added and the mixture is refluxed for one hour. The mixture is cooled and the crystalline plates removed by filtration and washed with 200 ml. of ethyl acetate.

Wt. 25 g. (56.0%) M.P. 198 - 202°C

	Calculated as $C_{10}H_{15}NCl_2$	Found
Carbon	54.55	54.65
Hydrogen	6.87	6.94

Bristol Laboratories
Research Division
Syracuse, New York
October 9, 1961

HLD/mal
994-14

THE LILLY RESEARCH LABORATORIES

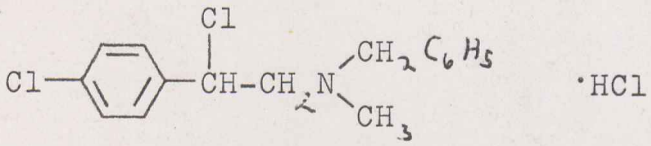
ELI LILLY AND COMPANY · INDIANAPOLIS, INDIANA 46206 · TELEPHONE (317) 636-2211

May 15, 1967

Mr. Van S. Hubbard
1175 Lenox Road
Schenectady, New York 12308

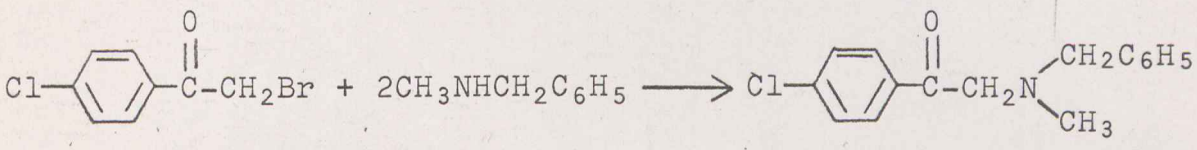
Dear Mr. Hubbard:

Dr. Slater referred your letter concerning the synthesis of

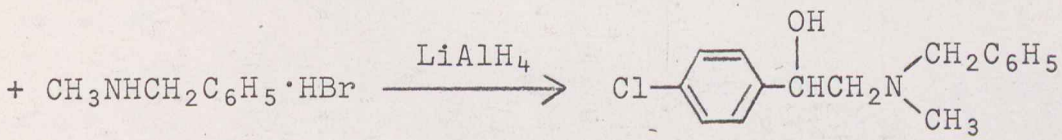


·HCl

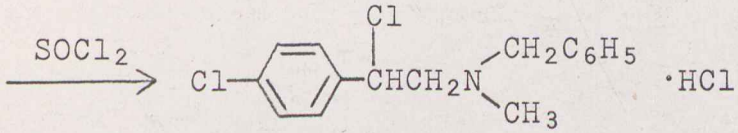
to me. We prepared this compound some seventeen years ago by the following reaction sequence.



(HCl salt, m.p. 199°)



(HCl salt, m.p. 163°)



(m.p. 154°)

If you are interested in attempting this route, I can send you detailed directions. We can make available small samples of the keto and carbinol intermediates if you need them for comparison. Our supply of the final product is exhausted.

In more recent years, we have preferred to use the bromohydrin route to compounds of this type. Unfortunately, your letter gave no details of the stoichometry or reaction conditions you employed in your attempted bromohydrin condensation. The insoluble material you obtained on dilution of the reaction mixture with ether is very probably methylbenzyl amine hydrobromide. Your desired product should be in solution as the base. I am at a loss to understand why you obtained only a small amount of the hydrobromide assuming your starting bromohydrin was a good quality. Possibly your conditions were not vigorous enough. We thoroughly mix the bromohydrin with three equivalents of the amine and an equal volume of ethanol. After refluxing vigorously for twelve hours, the mixture is poured into a large volume of dilute alkali and the organic layer is taken up in ether. After drying with magnesium sulfate the ether is removed and the residue gently heated under high vacuum to distill off excess benzylmethyl amine. The residue in the distillation flask is taken up in ether, filtered if necessary, and converted to the hydrochloride with gaseous HCl.

I hope the above method which we have used for many similar reactions will be of use to you.

Sincerely yours,

ELI LILLY AND COMPANY

Jack Mills

Jack Mills
Assistant to the Vice President
Research, Development, and Control

JM:ph

Bristol LABORATORIES
Division of Bristol-Myers Company
SYRACUSE, NEW YORK 13201

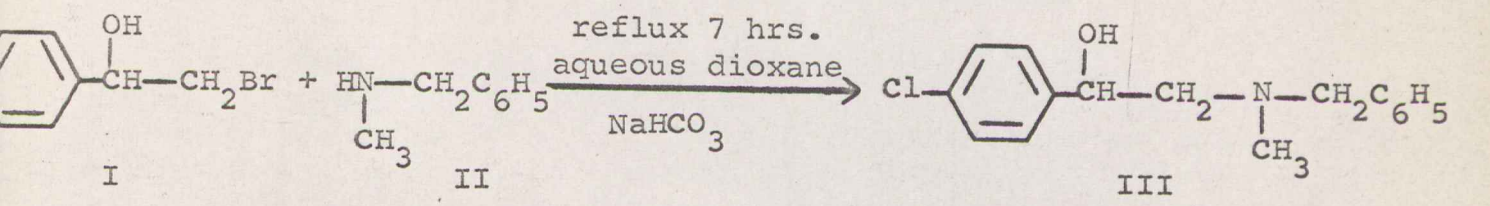
May 18, 1967

Mr. Van S. Hubbard
1175 Lenox Road
Schenectady, New York 12308

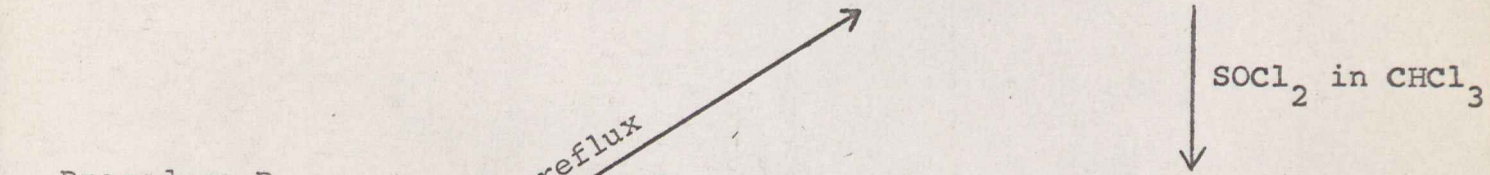
Dear Mr. Hubbard:

Your letter of May 9 to Dr. H.L. Dickison has been referred to my attention. We hope the following suggestions will prove helpful in your projected synthesis of compound IV.

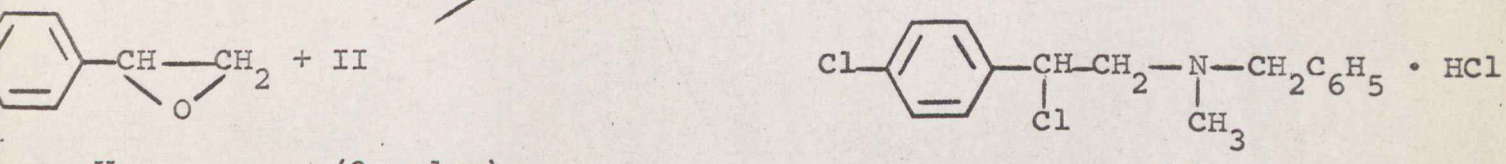
Procedure A



I II III



Procedure B



V (1 mole) (2 moles) IV

Perhaps your Method I failed because you did not use two molecular equivalents of N-methylbenzylamine (II). One molecular equivalent is required to serve as an acid-binding agent unless aqueous sodium bicarbonate is used for such a purpose. The following proposed procedure A is patterned after "Method B" of W.S. Emerson and E.P. Agnew, J. Am. Chem. Soc., 67, 518 (1945).

Procedure A for Preparing Amino Alcohol III. - Into a boiling, well stirred mixture of 0.2 mole of N-methylbenzylamine (II), 42 g. (0.5 mole) of sodium bicarbonate, 50 ml. of water and 200 ml. of dioxane (or tetrahydrofuran) add 0.2 mole of p-chlorostyrene bromohydrin (I) over a period of 30 minutes. After refluxing the stirred mixture for about seven hours, cool, dilute with about 800 ml. of water and extract the product with benzene. Distillation of the benzene extract should provide the amino alcohol III.

Alternative Procedure B for Preparing III. - Prepare p-chlorostyrene oxide (V) from p-chlorostyrene (Eastman) by the procedure used for making styrene oxide from styrene [Org. Syntheses, Coll. Vol. I, 494 (1941)]. Boil a mixture of 0.1 mole of V and 0.2 mole of N-methylbenzylamine under reflux for about five hours, and then distill the product to obtain III.

Conversion of Amino Alcohol III into the Desired β-Chloroethylamine Hydrochoride IV. To a stirred solution of 0.2 mole of III in 100 ml. of 100 ml. of chloroform add dropwise a solution of 0.26 mole of thionyl chloride (Eastman) in 50 ml. of chloroform. Then add 250 ml. of ethyl acetate and reflux the mixture for about one hour. Cool the mixture, collect the crystalline product (IV) by filtration. Wash the product thoroughly with cold ethyl acetate.

If additional help is required, please let us know.

Sincerely yours,

Lee C. Cheney, Director
Organic Chemistry Dept.

LCC/me

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(14) Lilly Research Laboratories. personal communication(1961).

(15) Lilly Research Laboratories. personal communication(1967).